Validation of Exercise-Enhanced Risk Assessment of Coronary Heart Disease Events: Longitudinal Changes in Incidence in Seattle Community Practice

ROBERT A. BRUCE, MD, FACC, LLOYD D. FISHER, PhD, FACC,
KENNETH F. HOSSACK, MB, BS, FACC

Seattle, Washington

Noninvasive criteria developed in a learning series for exercise-enhanced risk assessment for events due to coronary heart disease have been applied to a test series in a later population sample. Men in the same age and risk groups for each pretest clinical classification show similar gradients of risk. Thus, exercise-enhanced criteria for risk assessment are validated. Age-standardized event rates show a reduction longitudinally in healthy men and patients who have had coronary bypass surgery.

(J Am Coll Cardiol 1985;5:875–81)

Prior studies of the Seattle Heart Watch indicated the feasibility of symptom-limited maximal exercise testing by the Bruce protocol (1) in routine clinical practice (2). Effects of hypertension and coronary heart disease were separated from the concomitant physiologic consequences of aging (3). Clinical and noninvasive exercise predictors of sudden cardiac death have been identified (4), and the potential for noninvasive screening of patients with coronary heart disease for longer survival after coronary bypass surgery has been reported (5). Results of exercise-enhanced risk assessments of primary coronary heart disease events in healthy men (6), men with hypertension (7) and men with atypical chest pain syndromes (8) as well as the amount of risk enhancement (9) have been reported. (Two errors in that report should be corrected. The cumulative 5 year incidence rate in hypertensive men should be 18.2% rather than 33.3% as reported in the abstract, and survival rate without primary events in hypertensive men should be 81.8 ± 3.2%, as stated on page 570 of the text.) Furthermore, a pilot study (10) indicates that such testing motivates many individuals to modify risk factors.

The present study tests the hypothesis that criteria for exercise-enhanced risk assessment for coronary heart disease events are valid when applied to follow-up of a later population sample of men examined and tested noninvasively by physicians in Seattle community practice. Because of a reported 34% decrease in mortality due to coronary heart disease in the state of Washington, which exceeds the decrease in other states (11), longitudinal changes in mortality rates are also examined.

Methods

Study population. Salient clinical risk factor and exercise responses at enrollment, and subsequent follow-up findings in 5,308 men enrolled in the learning series of the Seattle Heart Watch during 1971 to 1974 are compared with findings in 3,065 other men enrolled in the test series* from 1975 to 1981 (12). Each year the institutional human subjects review committee reviewed and approved the study protocol and informed written consent forms of the subjects. Of the 8,373 men, 4,105 (49%) were classified before exercise testing as asymptomatic healthy individuals. The majority of these healthy men were from an industrial cohort and were voluntarily examined annually because of corporate policy; the remainder had presented to their physicians for a health assessment as described previously (6). Another 1,374 men had hypertension and 2,894 had prior

From the Department of Medicine and Department of Biostatistics, University of Washington, Seattle, Washington. This research was supported in part by contract and by research grants from the National Heart, Lung, and Blood Institute and the National Institute of Child Health and Development, Bethesda, Maryland, and a grant from the Bureau of Manpower, Health Resources Administration of the Department of Health, Education and Welfare, Washington, D.C. Manuscript received August 3, 1984; revised manuscript received October 23, 1984, accepted November 6, 1984.

Address for reprints: Robert A. Bruce, MD, Division of Cardiology, University Hospital, RG-22, Seattle, Washington 98195.

*The "test series" were men examined and exercised in an identical manner to the original participants in the Seattle Heart Watch Study. The same groups of physicians participated and initial clinical classification and subsequent classification of events were similar to those of the Seattle Heart Watch Study.

0735-1097/85/$3.30

clinical manifestations of coronary heart disease. The latter included typical angina pectoris, myocardial infarction, cardiac arrest or cardiac death. Almost all were white, urban and predominantly middle class persons.

Classification of risk. Risk was characterized as "low," "increased" or "high" for men free of clinical evidence of coronary heart disease. *Low risk* was defined by the absence of all conventional risk factors, as listed in Table 1. *Increased risk* was defined by the presence of any conventional risk factor and fewer than two exercise predictors for healthy men. Any conventional risk factor or exercise predictor indicated increased risk in hypertensive men. *High risk* was defined by the combination of one or more conventional risk factors and two or more exercise predictors in healthy men (6). In hypertensive men, high risk was defined by the combination of any risk factor and any exercise predictor. In men with coronary heart disease, risk was assessed by the pathophysiologic syndromes listed in Table 1.

Follow-up. Subsequent primary or secondary events due to coronary heart disease were ascertained periodically by questionnaires mailed to each individual. Funding to ascertain the role of vasectomy as a risk factor (13) provided only a single questionnaire follow-up in the test series in 1980 to 1981. This also included questions about any interventions to alter remediable risk factors (10).

Criteria for coronary events. The criteria for morbidity due to coronary heart disease have consistently been hospital admission for angina pectoris, coronary artery bypass surgery, acute myocardial infarction or sudden cardiac arrest with resuscitation by ventricular defibrillation (4–9). Cardiac mortality was classified as sudden when death occurred within 24 hours of symptoms, nonsudden if it occurred after the first day of symptoms or procedural if it was related to cardiac catheterization or cardiac surgery. (No deaths were reported in relation to exercise testing.) Information about the timing and circumstances of death was usually obtained from narrative descriptions from the next of kin to supplement medical records and death reports. Three cardiologists independently reviewed the data to classify these events.

Primary coronary events included all admissions to the hospital for the previously mentioned reasons. Secondary

Table 1. Criteria for Exercise-Enhanced Risk Assessments

Clinical Classification	Conventional Risk Factors	Exercise Risk Predictors
I. Healthy men (no symptoms, signs or treatment of cardiovascular disease)	1. Family history of myocardial infarction and/or sudden cardiac death in parents and/or siblings 2. Hypertension (systolic pressure of ≥140 mm Hg) 3. Hypercholesterolemia (total cholesterol of ≥250 mg/dl*) 4. Cigarette smoking	1. Chest pain during maximal exercise testing 2. Exercise duration <6 minutes or <stage III (of Bruce protocol) 3. Maximal heart rate <90% of age-predicted average normal value 4. ST segment depression of ≥1 mm, horizontal or downsloping for at least 1 minute or, if upsloping, for 3 minutes
II. Hypertensive men (history of prior hypertension without coronary heart disease, usually treated, or discovery of systolic blood pressure of ≥140 mm Hg)	1. Family history as stated for healthy men 2. Hypercholesterolemia 3. Cigarette smoking 4. Risk factor count	1. Chest pain during maximal exercise testing 2. Functional aerobic impairment of ≥25% which adjusts duration for age 3. Maximal heart rate <80% of age-predicted average normal value 4. Exercise predictor count
		Pathophysiologic Syndromes
III. Coronary heart disease (history of angina pectoris, myocardial infarction and/or sudden cardiac arrest from ventricular arrhythmia, with or without hypertension)	1. None contribute significantly to prediction	1. Exertional myocardial ischemia a. Chest pain during exercise testing b. ST segment depression of ≥1 mm usually beginning at submaximal work loads, increasing in magnitude at maximal exercise and evolving over several minutes in recovery 2. Left ventricular dysfunction: a. Cardiomegaly on examination b. Exercise duration <3 minutes or <Stage II, and/or c. Peak systolic pressure during exercise <130 mm Hg 3. Both syndromes 4. Neither syndrome

*In healthy men without cholesterol determinations, the incidence of coronary events did not exceed that for men without hypercholesterolemia (6). The same trend is observed in healthy men in the test series, of whom 564 had no reported cholesterol levels.

events were restricted to "hard" spontaneous events due to myocardial infarction, cardiac arrest or cardiac death. Hospital admissions for arteriographic evaluation or surgical treatment, or both, of angina pectoris were excluded because some were prompted by the patients' response to exercise testing.

Statistical methods. Variations in distribution of discrete variables were compared between groups using chi-square analysis for contingency tables. The occurrence of a first event was compared among groups using the life table method and the log rank test. The significance of longitudinal changes in age-standardized incidence of subsequent coronary events was computed by adjusting for three age intervals (<45, 45 to 54, ≥55 years) within each clinical classification and enhanced risk assessment group. The sum of combined registry populations (n = 8,373) was used as the reference group.

Results

Distribution of men at enrollment. Within each clinical classification, the distribution of men in the test series versus the learning series shows significant differences in relation to age and exercise-enhanced risk assessments (Table 2). There are more older men and more men at low risk among the healthy men in the test series. Yet the small proportion (1.1%) of healthy men at high risk is identical with the proportion in the learning series. Among hypertensive men, more are older and also at high risk. Whereas age differences are more significant than risk differences in healthy and hypertensive men, differences in distribution according to pathophysiologic syndromes are more significant than age differences in patients with coronary heart disease whether or not they have had coronary bypass surgery.

Variations in incidence of coronary heart disease events. The age-specific incidences of all primary and only "hard" secondary events due to coronary heart disease in relation to clinical classifications and risk categories are detailed elsewhere*. Comparison of these rates in the test series with those of the learning series reveals no statistically significant differences. Thus, the similarity of the risk gradients validates the criteria for exercise-enhanced coronary risk assessments in healthy men, hypertensive patients and nonsurgically treated patients with coronary heart disease. Inasmuch as several risk categories of patients with coronary heart disease who have had coronary bypass surgery do not, as yet, reveal any late morbidity or mortality, this treatment biases evaluation of the risk gradient.

Longitudinal changes in age-standardized incidence of coronary events. To adjust for differences in age distribution of men enrolled in the test series, age-standardized incidence was calculated for each risk group and clinical classification (Table 3). Three conclusions are apparent:

1) Lower event rates are observed in the test series in healthy men, in hypertensive men not at high risk and in men with coronary heart disease with either or both pathologic syndromes.

2) With the exception of healthy men at low risk and surgically treated men with coronary disease with these syndromes preoperatively, substantial and roughly similar mortality rates are found in all categories in the test series of men.

3) There is a reasonable question whether interventions may account for the reductions in incidence. More effective medical treatment and coronary bypass surgery, once pathophysiologic impairment is recognized, may be contributory in the patients, but these interventions do not fully account for changes in the healthy men.

Risk factor intervention in healthy men. Among 1,086 healthy men with one or more conventional risk factors, half (50.7%) reported one or more interventions. These included cessation of smoking, reduced ingestion of fat, loss of weight, increase of exercise and treatment of high blood pressure. (Details about date of onset of intervention, amount, duration and adherence are not available.) Eight events occurred in men reporting no intervention, including angina in two men (one with coronary bypass surgery) myocardial infarctions in two and cardiac deaths in four men aged 43 to 65 years. Six men were at increased risk with 50% case mortality, and two were at high risk with 50% case mortality. Only three events (angina) occurred in men of 42 to 54 years of age who reported any intervention. All three men were at increased risk and two of these had coronary bypass surgery; no deaths were reported. The annual incidence of these primary events was 0.52% for the nonintervention group and 0.19% for the intervention group. The first event in the latter group did not occur until 3 years had elapsed; when cumulative incidence was evaluated by life-table method, a log-rank statistic of 5.3 (with 2 degrees of freedom) indicated a significant decrease ($p < 0.05$).

Similar analyses of patients with hypertension and coronary heart disease did not reveal any effect of risk factor intervention.

Discussion

Significant findings. The results obtained in the test series indicate similar risk gradients for coronary heart disease events as reported earlier in healthy men and men with hypertension and coronary artery disease who are initially classified clinically and evaluated by risk factor, exercise risk predictors or pathophysiologic syndromes. Although risk of events increases with age and severity of cardiovascular impairment, age-specific incidences revealed no significant differences in all categories that could be evaluated.

*Data on file as NAPS Document no. 04620 for three pages of supplementary materials from ASIS/NAPS, Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, New York 10163.

JACC Vol. 5, No. 4
April 1985:875–81

Table 2. Variations in Distributions of Men

Registry	Learning Series n (%)		Test Series n (%)		
		Healthy			
Age (yr)					
<45	1,197 (50.6)		841 (48.3)		χ^2 = 56.1
45 to 54	926 (39.2)		583 (33.5)		2 df
≥55	242 (10.2)		316 (18.2)		p < 0.001
Risk					
Low	980 (41.4)		802 (46.1)		χ^2 = 8.98
Increased	1,360 (57.5)		919 (52.8)		2 df
High	25 (1.1)		19 (1.1)		p < 0.025
		Hypertensive			
Age (yr)					
<45	214 (30.3)		162 (24.3)		χ^2 = 22.42
45 to 54	297 (42.0)		240 (36.0)		2 df
≥55	196 (27.7)		265 (39.7)		p < 0.01
Risk					
Low	200 (28.3)		186 (27.9)		χ^2 = 6.84
Increased	398 (56.3)		343 (51.4)		2 df
High	109 (15.4)		138 (20.7)		p < 0.05
		Nonsurgically Treated Coronary Heart Disease			
Age (yr)					
<45	242 (15.6)		55 (11.2)		χ^2 = 23.49
45 to 54	643 (41.4)		163 (33.3)		2 df
≥55	670 (43.1)		272 (55.5)		p < 0.01
Syndromes					
Neither	597 (38.4)		234 (47.8)		χ^2 = 73.68
Myocardial ischemia	621 (39.9)		101 (20.6)		2 df
LV dysfunction	117 (7.5)		75 (15.3)		p < 0.001
Both	220 (14.1)		80 (16.3)		
		Surgically Treated Coronary Heart Disease			
Age (yr)					
<45	105 (15.4)		16 (9.5)		χ^2 = 23.85
45 to 54	316 (46.4)		53 (31.5)		2 df
≥55	260 (38.2)		99 (58.9)		p < 0.01
Syndromes					
Neither	104 (15.3)		50 (29.8)		χ^2 = 61.65
Myocardial ischemia	382 (56.1)		43 (25.6)		2 df
LV dysfunction	17 (2.5)		16 (9.5)		p < 0.001
Both	178 (26.1)		59 (35.1)		
Total	5,308 (63.4)	+	3,065 (36.6)	=	8,373 (100.0)

df = degrees of freedom; LV = left ventricular; n = number of men.

Thus, the criteria for exercise-enhanced risk assessment are considered validated. The report by Hopkirk et al. (14) also indicates the utility of sequential risk factors and exercise factors in the evaluation of normal subjects to identify individuals with significant coronary artery disease.

Despite significant differences in age and risk distributions, the age-standardized incidence of primary coronary events was lower in the test series except in hypertensive men at high risk. Age-standardized incidence of "hard" secondary events (that is, myocardial infarction and cardiac death) was lower in men with coronary heart disease who manifested exertional myocardial ischemia or noninvasive criteria (before any invasive data were available) of left ventricular dysfunction. Indeed, such patients who had coronary bypass surgery reported no morbidity or mortality up to the time of follow-up. More effective medical and surgical treatment may contribute to the apparent reduction in the incidence of secondary events. Exceptions to this trend are hypertensive patients at high risk and patients with coronary heart disease without these pathophysiologic syndromes.

Table 3. Age-Standardized Incidence of Coronary Events and Percent Mortality Rates*

Classification	Risk Group	Incidence (n, %/yr) Learning Series		Incidence (n, %/yr) Test Series		% Mortality Rates Learning Series	% Mortality Rates Test Series
All Primary Events in Men Without Coronary Heart Disease							
Healthy							
	Low	18	0.39	3	0.21	15.3	0.0
	Increased	43	0.54	9	0.23	12.1	41.0
	High	8	5.73	2	2.05	41.0	50.0
Hypertension							
	Low	11	0.77	4	0.50	9.1	50.0
	Increased	42	2.78	20	2.06	45.0	23.3
	High	26	3.71	19	4.51	42.0	35.6
"Hard" Secondary Events in Men With Coronary Heart Disease							
Nonsurgically treated							
	Neither	14	3.01	17	3.04	56.5	73.7
	Myocardial ischemia	133	3.74	6	1.50	59.5	75.3
	LV dysfunction	43	10.36	20	8.58	77.1	82.9
	Both	88	13.01	27	10.44	69.9	96.6
Surgically treated							
	Neither	4	0.79	3	2.42	45.6	37.1
	Myocardial ischemia	43	5.70	0	0.00	49.3	0.0
	LV dysfunction	4	7.45	0	0.00	20.1	0.0
	Both	13	1.93	0	0.00	82.4	0.0

*To adjust for significant differences in age distributions of all clinical groups defined in Table 1.

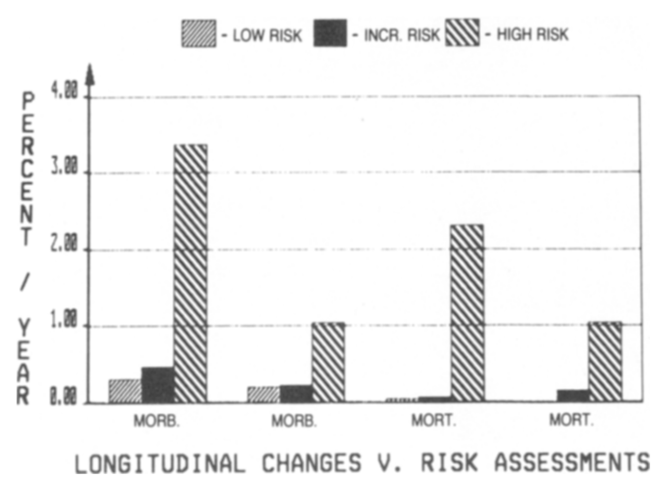
Whether the former group was overtreated or the latter group was treated prematurely cannot be ascertained from these data.

There is a provocative suggestion, however, in healthy men with risk factors that risk factor intervention may be effective in preventing primary coronary events. Only prolonged follow-up will reveal whether this effect merely postpones the occurrence of coronary events. Neither the initial classification of an active physical status nor the subsequent response to the questionnaire in regard to increased exercise revealed a statistically significant difference in incidence of coronary events.

Interaction of selection of a higher proportion of healthy men at low risk, despite a larger fraction of older men, and alleged interventions against remediable risk factors may account for the reduction in incidence of primary events in healthy men. Although this trend is consistent with a reported 34% decrease in mortality from coronary heart disease in the State of Washington (11), this statewide decrease reflects primarily mortality from secondary coronary events in patients with known coronary heart disease. Thus, the observed reduction in the number of patients treated medically or surgically is more likely to correlate with the statewide decrease in mortality.

Despite some decrease in the incidence of secondary events in patients with coronary disease, the apparent failure to observe a similar change in primary events in hypertensive men at high risk is provocative. This suggests that strategies for improving prognosis of hypertensive men might be reevaluated.

Figure 1. Longitudinal changes in age-standardized incidence of primary coronary heart disease (CHD) events in healthy men stratified according to initial risk assessment. Morbidity (MORB.) rates are separated from mortality (MORT.) rates; incidence rates for the learning series are shown on the **left** and incidence rates for the test series are shown on the **right**. Note the substantial reductions in both morbidity and mortality. INCR. = increased.



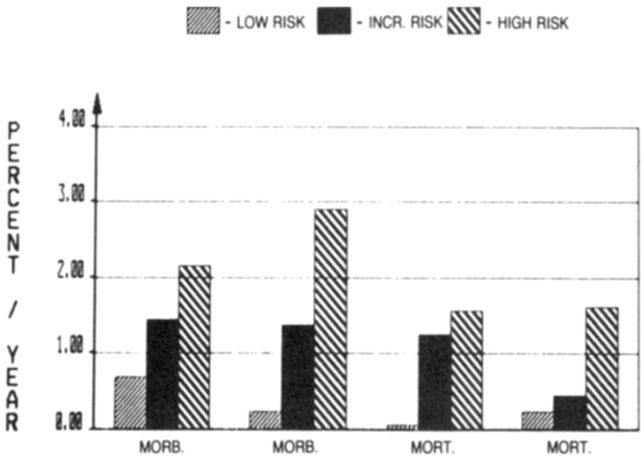
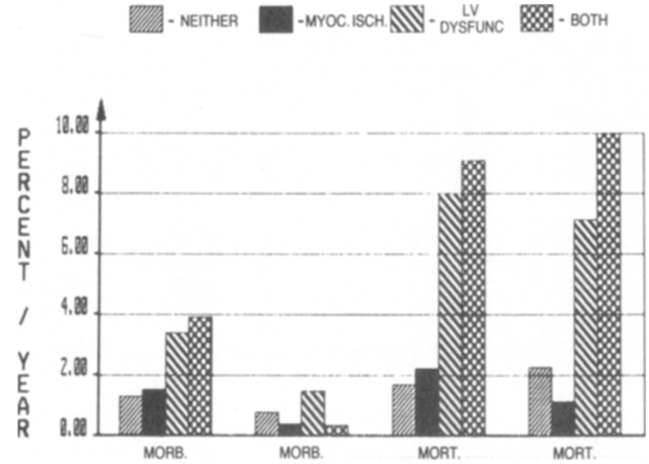


Figure 2. Longitudinal changes in age-standardized incidence of primary coronary heart disease events in hypertensive men stratified according to initial risk assessment. Morbidity (MORB.) rates are separated from mortality (MORT.) rates; incidence rates for the learning series are shown on the **left** and incidence rates for the test series are shown on the **right**. Note similarity of morbidity and mortality rates in test and learning series; see text for details.

Limitations of this study. Methodologic limitations should be noted. The majority of physicians failed to report serum cholesterol levels in all clinical categories. Yet the incidence of coronary events was always insignificantly lower in healthy men, hypertensive men and men with coronary heart disease in the test series. Thus, any loss of predictive value by this omission could not be established. Electrocardiographic monitoring may be considered suboptimal when only a single bipolar precordial lead was monitored continuously. Three considerations are noteworthy in this respect. An earlier study (15) involving computer averaging and quantitative analysis indicated that the information content of this lead closely approximated that of Frank orthogonal X, Y, Z leads. Only a single lead was commonly used in clinical practice during the early years of the study, and only a single lead could be transmitted by dataphone for independent computer analysis. Evaluation of more than 3,800 persons indicated that maximal differentiation of the ST response of patients with coronary heart disease from that of normal subjects occurred 1 minute after maximal exercise ($p < 0.00002$) (16).

Figure 3. Longitudinal changes in age-standardized incidence of hard secondary events due to coronary heart disease in men with coronary heart disease who remain without surgical treatment. They are stratified in relation to pathophysiologic syndromes: myocardial ischemia (MYOC. ISCH.) and left ventricular dysfunction (LV DYSFUNC). Morbidity (MORB.) rates are separated from mortality (MORT.) rates; incidence rates for the learning series are shown on the **left** and incidence rates for the test series are shown on the **right**. Note the substantial reduction in morbidity. Note that mortality rate exceeds morbidity rate.



Medical treatment could be a confounding variable. This data base was limited to drug treatment at the time of enrollment; subsequent variations in onset, amount, adherence to and duration of drug treatment over several years could not be ascertained. Of interest, the initial study (7) of hypertensive men reported an incidence of coronary events in 23.2/1,000 man-years in treated versus only 13.2/1,000 man-years for untreated patients (NS). The original aim of these studies was evaluation of responses to noninvasive exercise testing in addition to medical assessment of ambulatory persons in community practice. Another study involving appropriate experimental design (17) has applied serial exercise testing to evaluate the effects of prolonged treatment rather than predictive value of the initial exercise test.

Clinical implications. Symptom-limited maximal exercise testing for risk assessment for coronary heart disease events is useful in healthy men with one or more conventional risk factors, hypertensive men and ambulatory patients with coronary heart disease. Although criteria for exercise-enhanced risk assessment are not identical for all clinical categories, some individuals at high risk can be identified. When this sequential evaluation identifies men at high risk, further diagnostic studies and treatment are warranted. Nevertheless, the majority of events occur in men with only increased rather than high risk. Because of the provocative evidence for a reduction in incidence of coronary events in those who report risk factor intervention, more emphasis on intervention and, when indicated, medical treatment is warranted, whether or not exercise testing is performed to identify men at high risk.

We are indebted to numerous subjects, patients, physicians and data managers, particularly Verona Hofer, BS, who participated in these studies. The helpful critiques of Harold T. Dodge, MD and George N. Aagaard, MD are also acknowledged.

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